



Our STN: BL125772/0

**MID-CYCLE COMMUNICATION  
SUMMARY**

August 18, 2022

CSL Behring LLC  
Attention: Poorva Chiddarwar  
1020 First Avenue, PO Box 61501  
King of Prussia, PA 19406-0901

Dear Ms. Chiddarwar:

Attached is a copy of the summary of your July 19, 2022, Mid-Cycle Communication Teleconference with CBER. This memorandum constitutes the official record of the Teleconference. If your understanding of the Teleconference outcomes differs from those expressed in this summary, it is your responsibility to communicate with CBER as soon as possible.

Please include a reference to STN BL125772/0 in your future submissions related to etranacogene dezaparvovec.

If you have any questions, please contact Shalini Seetharaman at (240) 672-8158 or by email at [Shalini.Seetharaman@fda.hhs.gov](mailto:Shalini.Seetharaman@fda.hhs.gov).

Sincerely,

Steven S. Oh, PhD  
Acting Director  
Division of Cellular and Gene Therapies  
Office of Tissues and Advanced Therapies  
Center for Biologics Evaluation and Research

### Mid-Cycle Communication Teleconference Summary

**Application Type and Number:** BLA 125772/0  
**Product Name:** etranacogene dezaparvovec [HEMGENIX]  
**Proposed Indication for Use:** Treatment of adults with hemophilia B (congenital Factor IX deficiency) and (b) (4)

**Applicant:** CSL Behring, LLC  
**Meeting Date & Time:** July 19, 2022; 3:00PM to 4:30PM  
**Committee Chair:** Anurag Sharma, PhD  
**RPM:** Shalini Seetharaman, MS

#### FDA Attendees:

Emmanuel Adu-Gyamfi, PhD, CBER/OTAT/DCGT  
Esmeralda Alvarado Facundo, PhD, CBER/OCBQ/DBSQC  
Rachael Anatol, PhD, CBER/OTAT  
Marie Anderson, PhD, CBER/OCBQ/DBSQC  
Kimberly Benton, PhD, CBER/OTAT  
Wilson W. Bryan, MD, CBER/OTAT  
Dennis Cato, CBER/OCBQ/DIS/BMB  
Benjamin Cyge, CBER/OCBQ/DCM/APLB  
Varsha Garnepudi, PhD, CBER/OCBQ/DBSQC  
Denise Gavin, PhD, CBER/OTAT/DCGT  
Alifiya Ghadiali, PhD, CBER/OTAT/DMPQ  
Andrew Harmon, PhD, CBER/OTAT/DCGT  
Lin Huo, PhD, CBER/OBPV/DB  
Adnan Jaigirdar, MD, FACS, CBER/OTAT/DCEPT  
Megha Kaushal, MD, CBER/OTAT/DCEPT  
Margaret Benny Klimek, PhD, CBER/OTAT/DCEPT  
Carolyn Laurencot, PhD, CBER/OTAT/DCGT  
Wei Liang, PhD, CBER/OTAT  
Yuqun Abigail Luo, PhD, CBER/OBPV/DB  
Rommel Maglalang, CBER/OTAT/DRPM  
Ronit Mazor, PhD, CBER/OTAT/DCGT  
Bettina Joi McGraw, MD, CBER/OTAT/DCEPT  
Leyish Minie, MSN, RN, CBER/OTAT/DRPM  
Massoud Motamed, PhD, CBER/OTAT/DCGT  
Steven Oh, PhD, CBER/OTAT/DCGT  
Mikhail Ovanesov, PhD, CBER/OTAT/DPPT  
Tejashri Purohit-Sheth, MD, CBER/OTAT/DCEPT  
Shalini Seetharaman, MS, CBER/OTAT/DRPM  
Anurag Sharma, PhD, CBER/OTAT/DCGT  
Kimberly Schultz, PhD, CBER/OTAT/DCGT  
Abigail Shearin, VMD, PhD, CBER/OTAT/DCEPT

Ramani Sista, PhD, CBER/OTAT/DRPM  
Pan Tao, PhD, CBER/OCBQ/DBSQC/LAC  
Edward Thompson, CBER/OTAT/DRPM  
Triet Tran, PhD, CBER/OCBQ/DIS/BMB  
Natasha Thorne, PhD, CDRH/OPEQ/OHTVII/DIHD/HB  
Lori Tull, CBER/OTAT/DRPM  
Ramjay Vatsan, PhD, CBER/OTAT/DCGT  
Min Wu, PhD, CDRH/OPEQ/OHTVII/ DIHD/HB  
Lihan Yan, PhD, CBER/OBPV

### **CSL Behring Attendees**

Tara Chapman, North America Head, Global Regulatory Affairs  
Angela Mikroulis, North America Therapeutic Area Lead, Global Regulatory Affairs  
Poorva Chiddarwar, North America Regulatory Lead, Global Regulatory Affairs  
Scott Hambaugh, Head of Global Product Strategy, Global Regulatory Affairs  
Patrick Swann, Head of CMC, Global Regulatory Affairs  
Larissa Milke, Global CMC Lead, Global Regulatory Affairs  
Pedro Campino, Global Regulatory Lead, Global Regulatory Affairs  
John Blewitt, Global Regulatory Lead – Devices, Global Regulatory Affairs  
Paul Monahan, Senior Director, Clinical Development  
Yanyan Li, Director, Biostatistics  
Ling Chen, Associate Director, Biostatistics  
Michael Fries, Executive Director, Biostatistics  
Roberto Guillen-Gonzalez, Senior Director, Clinical Safety  
Kye Ehart, Senior Director, CMC  
Jacqueline Tarrant, Global Lead – Biomarkers, Clinical Development  
Jason Newman, Executive Director, CMC

### **Discussion Summary:**

1. Any significant issues/major deficiencies, categorized by discipline, identified by the Review Committee to date.

Chemistry Manufacturing and Controls (CMC):

- a. Extractables and Leachables (E&L): Insufficient data evaluating the E&L from the manufacturing process contact materials, (b) (4) drug product (DP) container closures have been submitted. We requested (filing letter dated May 23, 2022, and a follow-up information request (IR) dated June 17, 2022) you to conduct thorough E&L studies encompassing product manufacturing contact materials, (b) (4) DP container closures and provide analytical results. The issue regarding E&L testing has not been adequately addressed to date. Another follow-up IR was sent on July 14, 2022, requesting that you adequately address the E&L testing. We cannot complete our review without this information.

**Meeting Discussion:**

The applicant asked for additional clarification regarding the FDA's expectation for the evaluation of Extractables and Leachables (E&L). FDA stated that the applicant's evaluation for E&L is inadequate and potential presence of toxic E&L-related impurities in the drug product (DP) is a safety concern. The applicant is primarily focusing on the drug product container closure system for the assessment of E&Ls, and FDA wants the applicant to broaden their assessment to (b) (4) storage container and manufacturing contact materials as well. FDA also stated that the applicant should perform/ complete formal E&L studies to detect/identify the compounds and their concentrations, and the theoretical risk assessment alone is not sufficient.

The applicant acknowledged FDA's concerns and proposed to conduct a short-term E&L study representing worst-case scenario for the manufacturing contact materials and (b) (4) storage container. FDA stated that the applicant must submit the data from the proposed short-term study to the BLA prior to the action due date for the BLA. The data from the long-term study for the leachables may be provided post-BLA approval.

FDA suggested that the applicant submit the proposed study plan to the FDA for review and approval before initiating the study. The applicant agreed.

- b. (b) (4) activity control: The genomic titer (b) (4) assay protocol does not include a positive control for (b) (4) activity. Absence of this control may permit falsely high genomic titer results that could lead to errors in batch strength (vector genomes/ml) determination, and consequent errors in patient dosing. This could also result in errors for the calculations of impurities which is a safety concern. We requested this change in an IR dated June 17, 2022. We do not agree with your response dated July 01, 2022, that such a control is not necessary. A follow-up IR dated July 14, 2022, detailing the need for (b) (4) activity control for the (b) (4) assay was sent. This information is needed to complete our review of the BLA.
- c. In your response (dated July 01, 2022) to CMC IR (dated June 17, 2022) you acknowledged that the current analytical method validation package for the genomic copy assay does not address evaluation of the (b) (4) of the assay to potential sources of variability and you plan to address the (b) (4) of the assay by Q1 2023. We do not agree with your proposal as this assay is needed to control the vector dose and therefore, it should be fully validated prior to the BLA approval.
- d. Cumulative stability: The proposed shelf life for the DS is (b) (4) when stored at (b) (4). The proposed shelf life for the DP is 20 months when stored at +5°C ± 3°C. Insufficient stability data have been submitted to support cumulative stability of the DP after (b) (4) storage of the DS at - (b) (4) and 20 months of the DP at +5°C ± 3°C. An IR was sent (dated

July 14, 2022) requesting that you submit the stability data that demonstrates the cumulative stability. This data is needed to complete our review.

**Meeting Discussion:**

FDA clarified that the primary concern is the stability data to support the shelf-life of DP does not represent the worst-case scenario. FDA's expectation is the DP batches that are derived from aged DS batches should be used to support the shelf-life of the DP. The data provided in the BLA review utilizes relatively fresh DS batches to derive the DP.

The applicant asked for further clarification regarding the allowable DS and DP shelf-life. FDA stated that in the absence of supporting cumulative stability data, the maximal allowable DS shelf-life will be based on the duration for which the DS was stored prior to formulating into DP batches used to determine DP shelf-life. The DP shelf-life will be determined based on real-time stability data submitted/to be submitted in the BLA. At this stage FDA has not yet made a determination if the proposed shelf-life for DS and DP are acceptable. FDA also expects to receive additional stability data from the PPQ lots (primary stability data), as previously agreed upon. The applicant acknowledged.

- e. (b) (4) : The Applicant has proposed (b) (4) that are neither supported by real-time data from the Process Validation/Process Performance Qualification (PV/PPQ) runs or small-scale developmental studies. Specifically, the data from small scale and PPQ studies do not support the (b) (4) of the manufacturing process. An IR was sent (dated July 14, 2022) to submit additional data to support the in-process hold duration. This data is needed to complete our review.
- f. Assay (b) (4) : The validation studies for most of the analytical methods are not sufficiently comprehensive and are missing (b) (4) evaluations. An IR was sent (dated July 14, 2022) to adequately validate the assays for (b) (4) This data is needed to complete our review.

**Meeting Discussion:**

The applicant proposed to prioritize the assays and perform validation for (b) (4), starting with higher priority first and submit the results to the BLA. Validation for (b) (4) for some of the lower priority assays could be available post-BLA approval. FDA asked the applicant to submit the proposal to the FDA for review. The applicant agreed.

- g. (b) (4) potency assay: The proposed validated potency assay that measures (b) (4) is not sufficient because manufacturing consistency studies demonstrated the need for measuring FIX

(b) (4), by (b) (4), together with its (b) (4). The applicant was sent an IR (dated July 14, 2022) to validate their existing (b) (4) assay to measure transgene expression and develop release limits. This data is needed to complete our review.

#### Clinical

- h. Differences between the chromogenic and one stage Factor IX activity assays in patient plasma: This information was requested previously during the IND meetings and again in the filing letter dated May 23, 2022, as it is necessary for the assessment of proposed labeling. Please note that FDA has not been able to assess the acceptability of your factor assay discrepancy conclusions because this information was not provided in the initial BLA submission and your July 13, 2022, response to this deficiency was received after the internal mid-cycle meeting.

- i. We note that a Premarket Approval Application (PMA) (b) (4)

(b) (4)

We encourage you to work closely with your IVD companion diagnostic device partner to facilitate the contemporaneous approval of the BLA and the PMA.

#### Meeting Discussion:

The applicant inquired if CBER has made a determination regarding (b) (4) needed to validate the device performance. FDA stated this is currently under discussion.

The applicant acknowledged that the BLA review for the therapeutic product (b) (4) should be approved contemporaneously. Applicant inquired about possibility of a joint CDRH/CBER meeting with both the BLA (for the product) (b) (4). FDA noted that they will respond to the applicant following internal discussion.

#### Statistical:

- j. Please provide a comprehensive evaluation of the adequacy of the prophylaxis treatment each subject received during the lead-in period (i.e., baseline) and provide additional efficacy analyses accordingly if needed.

- i. The HOPE-B study uses a within-subject comparison design and therefore it is critical to have a well-defined and characterized population whose baseline will serve as control. The validity of the non-inferiority (NI) margin for the primary NI analysis also relies on all subjects having received adequate prophylaxis during the lead-in period to provide reliable baseline ABR for comparison.
- ii. FDA clinical review discipline previously provided related advice on the study population (FDA email May 19, 2021, Comment #2) regarding your defining “*continuous routine prophylaxis as the intent of treating with an a priori defined frequency of infusions as documented in the medical records.*” During the Application Orientation Meeting (April 29, 2022), we inquired about the adequacy of the lead-in period prophylaxis subjects received. To this you responded (May 10, 2022, BLA 125722/0 amendment 0006): “*Prophylaxis compliance during the Lead-in Period was not defined in the Clinical Study Protocol or Statistical Analysis Plan. In the Study CT-AMT-061-02 (HOPE-B) Clinical Study Report (CSR), Listing 2.2.2.1 provides prescribed FIX replacement therapy and Listing 2.2.2.2 provides FIX replacement injections (actual use) during the Lead-in and Post-treatment Periods.*”

Please note that evaluation of prophylaxis adequacy should encompass more considerations than just compliance with what has been prescribed to subjects, and that providing listings without critical evaluation is inadequate. FDA will issue a cross-discipline (clinical and statistical) information request outlining considerations in evaluating adequacy of prophylaxis each subject received during the lead-in period. FDA may request additional analyses depending on the result of this evaluation.

- k. Please provide a comprehensive evaluation of exogenous FIX replacement usage and specific reasons for all such occurrences post AMT-061 treatment, together with their potential confounding effect on the estimate of the AMT-061 treatment efficacy. Subjects’ original record should be verified and provided as part of this evaluation.
- i. While post-dosing FIX replacement use for reasons such as “routine prophylaxis” (prior to starting efficacy evaluation), “treatment of a bleed”, or “prophylaxis for surgery/invasive procedure” (when a specific surgery/invasive procedure was identified and occurred) is expected and interpretable in evaluating the AMT-061 treatment effect, we have identified two subjects where the recorded reasons for post-dosing FIX replacement usage do not include adequate information, and the usage patterns raise concerns on their confounding effect on the estimate of AMT-061 treatment efficacy.

- ii. You state that “*Following treatment with AMT-061, 52/54 (96.3%) subjects discontinued routine FIX prophylaxis and remained free of routine FIX prophylaxis from Day 21 through to Months 7 to 18.*” (HOPE-B CSR, p.7 of 166). You identify the two subjects who continued routine prophylaxis as Subject (b) (6) (who has the highest baseline anti-AAV5 NAb titer) and Subject (b) (6) (who received only 10% of the intended AMT-061 dose). However, there is at least one additional subject who appears to have used FIX prophylaxis starting 13 months after AMT-061 dosing (HOPB-B CSR, 14.3.3.4.1 Narratives for Bleeding Events and Surgeries, pp. 54-55 of 90): Subject (b) (6) received AMT-061 on (b) (6) and then received nine (9) exogenous FIX replacement infusions from (b) (6) at regular intervals with the use recorded as “*Selective prevention of a bleed*”, without any information in the narrative portion regarding these nine instances of FIX use.
- iii. For Subject (b) (6), there is inconsistency in reporting of post-dosing FIX use: the document 14.3.3.4.2 Individual Subject Narratives (p.185 of 351) states that “*The subject received 2 infusions of FIX replacement therapy on or after Study Day 21*”, while the document 14.3.3.4.1 Narratives for Bleeding Events and Surgeries reports 13 FIX infusions after Study Day 21 (AMT-061 treatment date: (b) (6)), with 10 infusions for “*Prophylaxis for invasive procedure*” from (b) (6) to (b) (6) (3 infusions on (b) (6)). There is no mention of what “invasive procedure” is in the latter document. This subject experienced a serious adverse event of hepatocellular carcinoma on (b) (6), which may explain the invasive procedures, but it is notable that such information is not mentioned in document 14.3.3.4.1 Narratives for Bleeding Events and Surgeries.

We recognize that exogenous FIX may be needed post AMT-061 administration for hemostatic challenges, e.g., prior to surgery or contact sports, or to reduce the likelihood of a bleed over and above the AMT-061 treatment effect. However, using on-demand/preventative FIX replacement for an upcoming bleed (not a true clinical bleed and therefore not documented as a bleeding event), e.g., when a subject feels a joint bleed coming on, will mask the inability of AMT-061 to prevent this potential bleed. In addition, frequent and regular FIX replacement use for vigorous activities will also confound the AMT-061 treatment effect. Therefore, we request the information listed at the beginning of this item. Depending on the result, we may request additional analyses to address concerns on the potential confounding effect of FIX use post AMT-061 administration.

- I. Please perform additional meaningful analyses on ABR, the primary efficacy endpoint, to account for subjects who use FIX replacement for routine



prophylaxis or other preventive purposes (excluding those for surgery or invasive procedure) during the efficacy evaluation period.

- i. Your current primary analysis on ABR removes time within 5 half-lives of a FIX infusion from the time at risk and then calculate ABR post dosing as the rate of “number of bleeds” over “time at risk”. This approach is reasonable when there is only a limited use of FIX infusions for treating bleeds or preventing bleeding during a surgery or invasive procedure. However, this approach is not reasonable for subjects using exogenous FIX for prophylaxis during the efficacy evaluation period after AMT-061 administration. When a subject did not stop or resumed routine prophylaxis, this approach masks the treatment failure of AMT-061 in this subject with the effect of the exogenous FIX.
- ii. The current approach can be anti-conservative, increasing the possibility of false positive results. Take Subject (b) (6) as an example. This subject did not respond to treatment with AMT-061 and was on prophylactic treatment, receiving 30 FIX injections during Months 7 to 18. Despite being on routine prophylaxis, this subject had five (5) spontaneous bleeds in this period, compared to zero bleeds during the lead-in period. The current approach yields a 1.09 day at risk time and correspondingly a post-dose ABR of 1674. However, because this subject contributes only 1.09 day at risk time relative to the ~ 365 days at risk time from most of the remaining 53 subjects in the primary analysis, the model yields a mean ABR of 1.51. If the ABR of 1674 has the same weight as those from the other subjects, the mean ABR would be >31.

For any subject using prophylaxis during the efficacy evaluation period of Months 7-18, one meaningful analysis would replace the bleed counts with what would be expected in the absence of the FIX replacement prophylaxis, i.e., what the bleed count would be when AMT-061 fails in this subject and there is only on-demand FIX replacement available. A range of possible values should be explored.

- m. Please submit subgroup analysis by geographical regions (US vs non-US).
  - a. Please submit efficacy subgroup analysis by geographical regions (US vs non-US), and critically evaluate potential influencing factors if a difference in efficacy is identified between the regions.

**Meeting Discussion:**

Applicant asked if the statistical comments will be sent an Information Request and it was confirmed by FDA that the request for response will be sent within a week.

2. Information regarding major safety concerns.

CMC

- a. Toxic E&L-related impurities may be present in the DP. This is a major safety concern (see comment #a of item #1).
- b. The absence of the control for (b) (4) activity may permit falsely high genomic titer results that could lead to errors in batch strength (vector genomes/ml) determination, and consequent errors in patient dosing. This could also result in errors for the calculations of impurities which is a safety concern (see comment #b of item #1).
- c. The high levels of (b) (4) concentration in the (b) (4) DP is a potential risk to patient safety (see comment #a of item #4).
- d. Additional information regarding the performance and validation of the in vitro assay for adventitious viral agents (AVA) is needed to assess the safety risk from AVA (see comment #b of item #4).

**Meeting Discussion:**

No further discussion.

3. Preliminary Review Committee thinking regarding risk management.

The review team has not identified a need for REMS at this time

**Meeting Discussion:**

No further discussion.

4. Any information requests sent, and responses not received.

CMC:

- a. The applicant was asked to evaluate the (b) (4) concentration in the drug product (IR dated June 17, 2022). The applicant commits to evaluate the (b) (4) concentration in the (b) (4) DP to further assess the potential risk to patient safety. Based on the (b) (4) analysis of the (b) (4) DP, and the corresponding risk, CSLB will evaluate the need to revise the supply chain for the sucrose currently used in the process. CSLB will provide details on the scope of analysis and anticipated dates for data receipt by September 2022.
- b. The applicant was asked to provide additional information regarding the performance and validation of the in vitro assay for AVA (IR dated June 17, 2022). The applicant has asked the vendor (responsible for performing in vitro

AVA testing) for additional information and a detailed response to this request will be subsequently submitted (response dated July 01, 2022). The applicant was asked to provide the expected timeline to submit their response (IR dated July 14, 2022).

- c. CMC IR dated July 14, 2022; due date July 28, 2022

**Meeting Discussion:**

The applicant requested an extension (email dated July 18, 2022) to respond to the CMC IR dated July 14, 2022 (due date July 28, 2022) by one week. FDA advised the applicant to split the responses in two parts and submit the acquirable responses by July 28, 2022, as requested. The remaining responses requiring more time, can be submitted by August 4, 2022. The applicant agreed.

- d. Clinical Safety IR dated July 15, 2022; due date July 22, 2022

**5. Any new information requests to be communicated.**

As review continues, new information requests will be conveyed as warranted

**Meeting Discussion:**

No further discussion.

**6. Proposed date(s) for the Late-Cycle meeting (LCM).**

- i. The LCM between you and the Review Committee is currently scheduled for September 30, 2022, from 10:00 AM to 11:30 AM
- ii. We intend to send the LCM meeting materials to you approximately 10 days in advance of the LCM.
- iii. If these timelines change, we will communicate updates to you during the review.

**Meeting Discussion:**

No further discussion.

**7. Updates regarding plans for the AC meeting.**

There are no plans currently to hold an Advisory Committee meeting for this application.

**Meeting Discussion:**

No further discussion.

8. Other projected milestone dates for the remainder of the review cycle, including changes to previously communicated dates.

- Tentative PMR/PMC Study and Labeling target date - Oct 21, 2022

**Meeting Discussion:**

No further discussion.

**End**